Environmental Health Perspectives
Vol. 86, pp. 155–158, 1990

OSHA's Approach To Risk Assessment for Setting a Revised Occupational Exposure Standard for 1,3-Butadiene

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In its 1980 benzene decision [*Industrial Union Department, ALF-CIO v. American Petroleum Institute*, 448 U.S. 607 (1980)], the Supreme Court ruled that "before he can promulgate *any* permanent health or safety standard, the Secretary [of Labor] is required to make a threshold finding that a place of employment is unsafe—in the sense that significant risks are present and can be lessened by a change in practices" (448 U.S. at 642). The Occupational Safety and Health Administration (OSHA) has interpreted this to mean that whenever possible, it must quantify the risk associated with occupational exposure to a toxic substance at the current permissible exposure limit (PEL). If OSHA determines that there is significant risk to workers' health at its current standard, then it must quantify the risk associated with a variety of alternative standards to determine at what level, if any, occupational exposure to a substance no longer poses a significant risk.

For rulemaking on occupational exposure to 1,3-butadiene, there are two studies that are suitable for quantitative risk assessment. One is a mouse inhalation bioassay conducted by the National Toxicology Program (NTP), and the other is a rat inhalation bioassay conducted by Hazelton Laboratories Europe. Of the four risk assessments that have been submitted to OSHA, all four have used the mouse and/or rat data with a variety of models to quantify the risk associated with occupational exposure to 1,3-butadiene. In addition, OSHA has performed its own risk assessment using the female mouse and female rat data and the one-hit and multistage models. While these risk assessments differ in the risks predicted at low doses, they all support OSHA's preliminary determination that there is significant risk of cancer from occupational exposure to 1,3-butadiene at the current OSHA PEL of 1000 ppm. OSHA plans to publish a proposal to revise the current 1,3-butadiene standard. In addition, OSHA will publish a request for public comment on the proposal. OSHA's final standard will be based on its evaluation of the public record and will be guided by significant risk determination.

The Occupational Safety and Health Act of 1970 spells out the mandate of the Occupational Safety and Health Administration (OSHA) for assuring safe and healthful working conditions for working men and women (*1*). In section 6(*b*)(5) of the Act, Congress directed that the Agency, "in promulgating standards dealing with toxic materials or harmful physical agents, . . . shall set the standard which most adequately assures, to the extent feasible, on the basis of the best available evidence, that no employee will suffer material impairment of health or functional capacity even if such an employee has regular exposure to the hazard dealt with by such a standard for the period of his working life." In Section 3(8), Congress defined "occupational safety and health standard" as "a standard which requires conditions, or the adoption or use of one or more practices, means, methods, operations, or processes reasonably necessary or appropriate to provide safe or healthful employment or places of employment."

Based on the belief that any exposure to a carcinogen, regardless of the level, is not safe, OSHA originally interpreted Congress's directive as meaning that occupational exposure to carcinogens should be regulated down to the lowest feasible level. In 1980, the Supreme Court rejected this interpretation of the Act in its benzene decision (*2*). The Court ruled that "before he can promulgate *any* permanent health or safety standard, the Secretary [of Labor] is required to make a threshold finding that a place of employment is unsafe—in the sense that significant risks are present and can be lessened by a change in practices" (448 U.S. at 642).

The Supreme Court did not define "significant risk" in its ruling, but it did offer some guidelines. The Court wrote that "if the odds are one in a billion that a person will die from cancer by taking a drink of chlorinated water, the risk clearly could not be considered signifi-

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cant. On the other hand, if the odds are 1 in a 1000 that regular inhalation of gasoline vapors that are 2% benzene will be fatal, a reasonable person might well consider the risk significant and take appropriate steps to decrease or eliminate it" (448 U.S. at 655). The Court went on, however, to say that "OSHA is not required to support its finding that a significant risk exists with anything approaching scientific certainty . . . so long as they are supported by a body of reputable scientific thought, the Agency is free to use conservative assumptions interpreting the data with respect to carcinogenicity risking error on the side of over-protection rather than under-protection" (448 U.S. at 656).

OSHA has interpreted the Supreme Court's ruling to mean that it must perform quantitative risk assessments whenever possible in order to determine whether occupational exposure to a toxic substance poses a significant risk to workers. If OSHA determines that a significant risk exists, then it must quantify the risk associated with a variety of alternative standards to determine at what level, if any, occupational exposure to a substance no longer poses a significant risk.

The current OSHA standard for 1,3-butadiene is 1000 parts per million (ppm) determined as an 8-hr time-weighted average (*3*). Adopted in 1971, this standard was aimed at preventing irritation and necrosis. Since that time, two animal bioassays have shown that 1,3-butadiene exposure induces cancer in rodents. The two studies, an inhalation bioassay conducted by the National Toxicology Program (NTP) using $B6C3F_1$ mice (*4*) and an inhalation bioassay conducted by Hazelton Laboratories Europe (HLE) using CD rats of the Sprague-Dawley strain (*5*), demonstrated a dose-response relationship between exposure and carcinogenesis. In addition to this evidence of the carcinogenicity of 1,3-butadiene, four epidemiological studies have been conducted that show elevated death rates due to lymphohematopoietic cancers among workers exposed to 1,3-butadiene (*6–9*).

Following the Supreme Court's Benzene decision, OSHA must first determine whether workers face significant risk of cancer at exposures of 1000 ppm before it can consider reducing the current standard. In order to make this determination, OSHA reviews the public record and evaluates research and analyses on the occupational risk of 1,3-butadiene exposure. OSHA uses the research of others to develop its own preliminary assessment of risk. This assessment is published with a proposal for a revised standard. At that time, OSHA's assessment may be evaluated by scientists and interested parties outside of the Agency, and anyone may comment on the assessment.

For the rulemaking on 1,3-butadiene, five risk assessments have been submitted. Two of these are from the U.S. Environmental Protection Agency; one is from the Office of Toxic Substances (OTS) (*10*), and the other is from the Carcinogenicity Assessment Group (CAG) (*11*). A third risk assessment was performed under contract to OSHA by ICF/Clement Association (ICF) (*12*), and a fourth was performed under contract to the Chemical Manufacturers Association by Environ Corporation (*13*). The National Institute of Occupational Safety and Health (NIOSH) has recently submitted a fifth risk assessment that was performed by D. Hattis and J. Wasson at the Center for Technology, Policy and Industrial Development at the Massachusetts Institute of Technology (*14*). OSHA is currently reviewing this assessment which is a pharmocokinetic/mechanism-based analysis of the carcinogenic risk of 1,3-butadiene.

All of these risk assessments relied on the animal bioassay data for quantifying carcinogenic risk. While there is less uncertainty in extrapolating risks from human data, none of the available epidemiological studies provide adequate exposure data for such an assessment. Therefore, risk assessments must rely upon the animal data for their analyses. Both bioassays have the advantage that the route of exposure is the same as the one found in occupational settings (i.e., inhalation), the animals were exposed to at least two different levels of the test substance, and concurrent controls were used. In addition, data on the absorption of 1,3-butadiene in both mice and rats are available and can be used to estimate internal dose (*15*).

Extrapolating risks from animals to humans entails five steps before risks may be estimated. Choices made by a risk assessor at each of these steps will affect the outcome of a risk assessment, and therefore OSHA's evaluation of a quantitative risk assessment centers on these choices. All of the risk assessments submitted to OSHA differ in the choices made.

The first step in performing a quantitative risk assessment entails choosing a data set for low-dose extrapolation. OTS and ICF considered only the male and female mice; CAG used the males and females of both species; and Eviron used the male and female rats but only the male mice.

Although exposure levels are determined in the design of a bioassay, the risk assessor must choose an appropriate measure of experimental dose when extrapolating risks across species. OTS and ICF measured dose in parts per million, but ICF adjusted for absorption while OTS did not. Both adjusted for early termination of the study, but OTS made this adjustment to dose while ICF made this adjustment to risk. CAG and Environ measured dose in milligrams per kilogram per day and adjusted experimental dose for absorption.

The risk assessor must also choose an appropriate measure of response. It is in this respect that the risk assessments reviewed by OSHA differ most. While all the risk assessments considered pooled tumor incidence as its measure of carcinogenic response, different tumor incidences were used to form the pool. This is especially true for the analyses of the rat data; each person counting tumors from the individual pathology reports seemed to have a different estimate of tumor incidence. Pooled tumor incidence among the mice, however, also differed from risk assessment to risk assessment. OTS used life-table adjusted incidence. CAG and ICF used all

tumors reported by NTP as occurring at a statistically significantly elevated rate in exposed mice, but ICF excluded papillomas of the forestomach. In addition to looking at pooled tumor incidence, OTS and ICF considered site-specific tumor incidence as a measure of carcinogenic response in the mouse.

The fourth step in performing a quantitative risk assessment is to convert occupational dose into units comparable to those in which experimental dose is measured. While each risk assessment used different assumptions and exposure scenarios, OSHA assumed that the average worker weighs 70 kg, breathes 9.6 m^3 of air during an 8-hr shift, and works 8 hr/day, 250 days/year, for 45 out of 74 years of life.

Occupational dose must also be adjusted for absorption. OTS assumed 100% absorption in humans regardless of dose, and CAG and Environ assumed 54% absorption in humans regardless of dose. ICF assumed that absorption in humans varied with dose at the same rate it varied with dose in the mice.

Finally, in any quantitative risk assessment, the choice of mathematical model used for extrapolating risks observed in the high-dose range to risks associated with exposure at lower doses will effect the magnitude of predicted risks. Models fall into two types: mechanistic and tolerance distribution. The most popular mechanistic model is the multistage model, based on a theory proposed by Armitage and Doll in 1961 (*16*). The multistage model is based on the biological assumption that cancer is induced by carcinogens through a series of stages. The one-hit model is a special case of the multistage model and is based on the assumption that there is only one stage in the carcinogenic process. OTS, CAG, and ICF used only the multistage model to extrapolate risks. Tolerance distribution models, such as the probit model and logit model, attempt to describe the distribution of tolerances (i.e., exposure levels below which no response occurs) in an exposed population. Environ considered some of these models in addition to the multistage model.

After OSHA reviewed the submitted risk assessments, it performed its own preliminary analysis of the risk associated with occupational exposure to 1,3-butadiene. Like the others, OSHA has relied on the animal data in its assessment. Experimental dose was measured in miligrams per kilogram per day and adjusted for absorption. Risks were derived using both pooled tumor and site-specific tumor incidence data with the multistage model. OSHA has consistently evaluated several models when performing quantitative risk assessments, but it has shown a preference for the multistage model. The Agency has justified this preference on the grounds that the multistage model has the best empirical and theoretical justification for use in making "best estimates" of likely risk at specific doses. Furthermore, the multistage model is a conservative, nonthreshold model, and OSHA believes that its application in quantitative risk assessment is prudent public health practice.

Table 1 presents risk estimates from OSHA's preliminary analysis as well as from the risk assessments by OTS, CAG, ICF, and Eviron. Estimates are presented as deaths per 10,000 for occupational exposure to 100 ppm—a level 10 times lower than the current OSHA standard. These numbers were either calculated in the risk assessments submitted to OSHA or derived from those risk assessments. Presented are those risks associated with exposure scenarios most closely resembling the scenario chosen by OSHA.

In their risk assessments, OTS and ICF presented only the 95% upper confidence limits (UCLs) for a variety of exposure scenarios. OSHA calculated the maxi-

Table 1. Estimates of cancer risk to workers with lifetime occupational exposure to 100 ppm 1,3-butadiene.[a]

Source	*Date*	*Model*	*Risk per 10,000*
OSHA	Pooled female mouse tumors[b]	Multistage	180 (1300)
OSHA	Female mouse hemangiosarcomas	Multistage	443 (610)
OSHA	Pooled female rat tumors[c]	One-hit	1272 (1685)
OTS	Pooled male mouse tumors	One-hit	8843 (9683)
OTS	Pooled female mouse tumors	One-hit	5752 (6740)
OTS	Male mouse hemangiosarcomas	One-hit	3298 (4347)
CAG	Pooled male and female mouse tumors[d]	Multistage	7930 (8597)
CAG	Pooled male rat tumors	Multistage	208 (610)
CAG	Pooled female rat tumors	One-hit	4595 (5563)
ICF	Pooled male mouse tumors[e]	One-hit	10,000 (10,000)
ICF	Pooled female mouse tumors	Multistage	10,000 (10,000)
Environ	Pooled male mouse tumors[b]	Hartley-Sielken	3730 (4260)
Environ	Pooled male rat tumors[f]	Multistage	210 (682)
Environ	Pooled male [f] rat tumors	Weibull	154 (571)
Environ	Pooled male rat tumors[f]	Mantel-Bryan	559 (847)
Environ	Pooled female rat tumors[g]	Multistage	575 (794)
Environ	Pooled female rat tumors[g]	Weibull	560 (763)
Environ	Pooled female rat tumors[g]	Mantel-Bryan	730 (1040)

Abbreviations: OSHA, Occupational Safety and Health Administration; OTS, Office of Toxic Substances; CAG, Carcinogenic Assessment Group; ICF, ICF/Clement Association; Environ, Environ Corporation.

[a]Risk estimates are the maximum likelihood estimates (MLEs). Numbers in parentheses are the 95% upper confidence limits (UCLs).

[b]Incidence of lymphoma excluded from pooled tumor incidence.

[c]High-dose group dropped from the analysis.

[d]Maximum likelihood estimates (MLE) and upper confidence limits (UCL) are the geometric mean of the MLEs and UCLs estimated from male mouse data and female mouse data.

[e]Model is the Hartley-Sielken time-to-tumor model.

[f]Incidence of Zymbal gland carcinoma excluded from pooled tumor incidence.

[g]Incidence of mammary fibroadenoma excluded from pooled tumor incidence.

mum likelihood estimates (MLEs) associated with these 95% UCLs for exposure of 8 hr/day, 240 days/year. For OTS, exposure was for 40 out of 70 years; for ICF, exposure was for 45 out of 70 years.

CAG focused its risk assessment on estimating the unit risk associated with 1,3-butadiene exposure. OSHA derived estimates of risk from the CAG risk assessment using the equality 1 ppm = 2.25 mg/m^3 and CAG's assumptions that exposure occurred 8 hr/day per day, 240 days/year, for 45 out of 70 years; that a 35-g mouse breathes 0.043 m^3 of air/day; that a 0.70-kg rat breathes 0.354 m^3 of air/day; and that absorption at low doses is 54%. Risks were estimated using the computer program GLOBAL 82 (*17*). Following CAG, OSHA calculated the geometric mean of the MLEs derived individually from the male mouse data and the female mouse data. The same was done for the UCLs. CAG reasoned that because response was so similar between male and female mice, the geometric mean of the risks was an appropriate estimate. While CAG adjusted its estimate of unit risk for early termination of the NTP study, the numbers in Table 1 were not adjusted.

Table 1 shows that regardless of which animal bioassay is used, how the experimental or occupational dose is calculated, what the measure of carcinogenic response is, and any other adjustments made to the data, the risk associated with occupational exposure to 100 ppm 1,3-butadiene over a working lifetime is well in excess of the 1 per 1000 cited by the Supreme Court as constituting significant risk. This exposure level is 10 times lower than the current OSHA standard. The highest risks are predicted by ICF. The ICF estimates exceed 100% risk because of the adjustment made for early termination of the study. The lowest risk, 154 per 10,000, was predicted by Environ using the mechanistic Weibull model applied to the male rat pooled tumor incidence data.

OSHA has preliminarily stated that occupational exposure to 1,3-butadiene poses a significant risk. In addition to demonstrating a health need for a standard, however, OSHA's standards must be economically and technologically feasible; to that end, it has contracted for an economic and engineering survey of the industries affected by the standard. Given preliminary reports of feasibility, OSHA is proceeding with the publication of a proposal for a revised standard. Following publication, there will be a comment period and then informal hearings will be held. OSHA's final standard will be based upon its evaluation of the public record and will be guided by the Supreme Court's Benzene decision on significant risk determination.

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